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A rare agent; Growth of *Elizabethkingia Meningoseptica*, 11 years of evaluation

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Abstract

Aim: In this study, we aimed to present *E. meningoseptica* infections, which grew on the cultures of inpatients in our hospital's various clinics.

Material and Methods: All patients with a positive culture of *E. meningoseptica* admitted to our hospital between April 2008 and July 2019 were retrospectively included in this study. Demographic data, clinical diagnosis, outcomes and antimicrobial susceptibility for all isolates were extracted from patient electronic medical records.

Results: Over an 11-year period, seventeen patients have been infected with *E. meningoseptica* in our hospital. Most of them (n:11) were from intensive care units (ICU). Eight of the samples from which growth detected, were blood, 6 were endotracheal aspirate, 2 were cerebrospinal fluid, and 1 was wound swab. Most of them were children (76%). Cefoperazone/sulbactam, ciprofloxacin and trimethoprim/sulfamethoxazole were found to be the most effective antibiotics.

Discussion: *E. meningoseptica* is usually isolated as hospital acquired infection. It can make outbreaks in ICUs and also can be isolated from individual cases. Variable mortality rates of the infection have been reported. *E. memingoseptica* is resistant to antibiotics frequently used in the treatment of gram-negative infections as carbapenems, beta-lactams and aminoglycosides. In contrast to previous studies, we found lower susceptibility rates (18.1%) against piperacillin/tazobactam. This infection should be kept in mind for patients at risk group who do not respond to treatment.

Keywords

Elizabethkingia Meningoseptica; Hospital infection; Antibiotic resistance

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Introduction

Elizabethkingia meningoseptica (Chryseobacterium meningosepticum), formerly known as *Flavobacterium meningosepticum*, is a rod-shaped gram-negative bacterium that is widespread in nature (for example, in water, plants and soil). Many environmental studies have shown that *E. meningoseptica* can survive in chlorine-treated municipal water supplies, often colonizing sink basins and taps, and has become a potential reservoir of infections in the hospital environment. Organisms have been recovered from dialysis systems, pharmaceuticals, and medical devices (including intravascular catheters, respirators and intubation tubes) [1]. They do not normally exist in the human body, but have been reported to cause various invasive infections like meningitis, pneumonia, endocarditis, and bacteremia in adults and neonates in association with a severe underlying illness [2]. It usually has low virulence and is prone to infecting newborns and immunocompromised hosts. It can also cause nosocomial outbreaks, especially in critical care and neonatal units, and these are difficult to control. Risk factors associated with acquiring this infection include immunosuppression, underlying medical diseases, prolonged hospital stay, prior use of higher antibiotics, indwelling central venous catheter and other invasive devices [3]. This organism is resistant to many antibiotics like beta-lactam antibiotics, aminoglycosides, tetracyclines, and chloramphenicol [2]. Many possess two different types of β-lactamases, namely class A extended-spectrum β-lactamases and class B metallo-β-lactamases (MBLs); the latter confer resistance to carbapenems, which are widely used to treat infections caused by multidrug-resistant gram-negative bacteria. Two types of MBL, BlaB and GOB, have been identified in isolates of *E. meningosepticum*. They are constitutively resistant to multiple antibiotic classes and has unusual resistance patterns and mechanisms [4]. The selection of appropriate antimicrobial agents for patients infected with *E. meningoseptica* is difficult due to the lack of data on the clinical response to different treatments, as well as due to multiple drug resistance [2].

In this study, it was aimed to present the infections of *E. meningoseptica* which have grown on the cultures of inpatients in our hospital's various clinics.

Material and Methods

All patients with a positive culture of *E. meningoseptica* admitted to our hospital between April 2008 and July 2019 were retrospectively included in this study. Demographic data, clinical diagnosis, outcome and antimicrobial susceptibilities for all isolates were extracted from patients electronic medical records. Moist grey and white colonies on blood agar and, typically lactose-negative small colonies on EMB agar are picked up. Identification of isolates was done using conventional methods, the VITEK 2 Compact (bioMerioux, France) automated system and MALDI-TOF MS (Bruker, Germany). Susceptibility testing was performed for all isolates using the Kirby-Bauer disc diffusion method and the VITEK 2 Compact (bioMerioux, France) automated system according to the CLSI and EUCAST standards. When repetitive growth was found, only the first strain of each patient was included in the study.

Results

Over an 11-year period, seventeen patients have been infected with *E. meningoseptica* in our hospital. Most of them (n:11) were from intensive care units (ICU). Eight of the samples from which growth detected were blood, 6 were endotracheal aspirate, 2 were cerebrospinal fluid and 1 was wound swab. Except for one patient (whose blood culture was positive for *E.meningoseptica* on the first day of admission to the hospital), the mean-time from admission to the isolation of *E.meningoseptica* was 50 days range (5-162 days) .All the patients had long term hospitalization (mean: 71 days, from 19 to 187 days) and had various underlying diseases. Only one of thirteen pediatric patients and all four adult patients died. According to the antibiograms of the strains, the most effective antibiotics were cefoperazone/sulbactam, ciprofloxacin and trimethoprim/sulfamethoxazole.

The clinical characteristics of the patients (Table 1) and antibiotic susceptibilty of the strains (Table 2) are presented in the tables.

Discussion

E. meningoseptica are isolated primarily as hospital acquired infection agents and can cause outbreaks, especially in ICUs. It has been observed that the number of patients with *E. meningoseptica* bacteremia is increasing; indeed, at a medical center in Taiwan, the incidence (per 100,000 admissions) of *E. meningoseptica* bacteremia increased from 7.5 in 1996 to 35.6 in 2006 [5]. The incidence of *E. meningoseptica* bacteremia in the present series was not associated with a hospital outbreak, and we did not observe any increase by years. This may be because of the successful implementation of infection control program in our hospital, isolation precautions, and a hand hygiene program. *E. meningoseptica* infection in humans is usually acquired in the hospital and is most likely associated with the presence of invasive equipment, treatment with long-term broad-spectrum antibiotics, or long periods of hospitalization [1,5]. Ratnamani et al. reported eight patients infected with *E. meningoseptica* in their hospital over a 6-month period. All were on mechanical ventilation and bedside hemodialysis in ICU [4]. Weawer et al. reported nineteen patients on mechanical ventilation and infected with *E.meningoseptica* in ICU and eight died [6]. In our study, patients with severely debilitating diseases who had ICU admission and received antibiotics during a long period of hospitalization were at high risk for *E. meningoseptica* infection.

In previous studies, *E. meningoseptica* outbreaks have been reported, and pediatric patients, especially neonates and premature infants, are at great risk for *E. meningoseptica* infection [7,8]. Lin et al. searched the relationship between 28 isolates of *E. meningoseptica*, which they collected over a 3-year period, by pulsed-field gel electrophoresis. They demonstrated that most of the isolates were epidemiologically unrelated [9]. In the present study, however, we had a neonates clinic in our hospital, all of our patients were older pediatric and adult individuals. Unfortunately, we could not have any molecular analysis of the isolates, to detect if any relationship existed between them, as it is one major limitation of our study.

Table 1. Clinical characteristics of the patients

Case	Age	Gender	Date	Sample	Location	Underlying Disease	Clinical Diagnosis	Outcome
1	71	M	2008	Blood culture	ICU	Cerebrovascular Disease, Lung Edema, Tracheostomy	Bacteremia	Exitus
2	3	F	2009	Blood culture	Pediatric ICU	Acute Lymphoblastic Leukemia	Febrile Neutropenia	Recovered
3	69	M	2012	Blood culture	Anesthesia ICU	Chronic Obstructive Lung Disease, Chronic Renal Failure, Hemodialysis	Bacteremia	Exitus
4	6 months	F	2012	Endotracheal aspiration fluid culture	Pediatric ICU	Epilepsy	Bronchopneumonia	Recovered
5	3	M	2013	Blood culture	3. Pediatric Clinic	Acute Disseminated Encephalomyelitis	Septicemia	Recovered
6	2	M	2013	Endotracheal aspiration fluid culture	Pediatric ICU	Epilepsy, Joubert Syndrome	Septicemia	Exitus
7	3 months	F	2013	Blood culture	4. Pediatric Clinic	Cystic Fibrosis, Aganglionic Bowel, Colostomy	Septicemia	Recovered
8	5 months	F	2014	Endotracheal aspiration fluid culture	Pediatric ICU	Arnold Chiari Syndrome, Hydrocephalus	Septicemia	Recovered
9	2	M	2015	Wound swap culture	Pediatric Gastroenterology Clinic	İleus, Chronic Diarrhea	Septicemia	Recovered
10	5	M	2015	Blood culture	Pediatric ICU	Atrial Septal Defect	Septicemia	Recovered
11	40	F	2016	Endotracheal aspiration fluid culture	Anesthesia ICU	Operation because of Aortic Dissection , Acute Renal Failure	Septicemia	Exitus
12	4	F	2016	Blood culture	Pediatric ICU	Cerebral Palsy, Epilepsy	Aspiration pneumonia, Septicemia	Recovered
13	5 months	F	2017	Cerebrospinal fluid	Nurseling Clinic	Hydrocephalus, Acute Renal Failure	Meningitis, Ventriculoperitoneal Shunt Infection	Recovered (Transferred to another hospital on family's request)
14	1	M	2018	Cerebrospinal fluid	Nurseling Clinic	Hydrocephalus	Meningitis, Ventriculoperitoneal Shunt Infection	Recovered
15	17	F	2018	Endotracheal aspiration fluid culture	Pediatric ICU	Cerebral Palsy, Acute Renal Failure, Tracheostomy	Septicemia	Recovered
16	1	M	2019	Blood culture	Nurseling Clinic	Trizomy 21, Hirschsprung Disease, Colostomy	Septicemia	Recovered
17	65	F	2019	Endotracheal aspiration fluid culture	Anesthesia ICU	Encephalopathy, Acute Renal Failure	Cerebrovascular Disease	Exitus

M: Male, F: Female ICU: Intensive Care Unit

Table 2. Antibiotic susceptibilty of the strains

Case	Ceftazidime	Cefepime	Cefoperazone-sulbactam	Piperacillin-tazobactam	Amikacin	Gentamicin	Trimethoprim-sulfamethoxazole	Ciprofloxacin	Imipenem	Meropenem
1	R	R	-	R	R	R	R	S	-	-
2	R	R	-	-	R	R	R	R	R	I
3	-	R	S	-	-	-	R	S	R	R
4	R	R	S	-	-	-	-	S	R	R
5	-	S	S	-	S	R	S	-	R	R
6	R	R	-	-	-	-	R	S	R	R
7	R	R	S	-	-	-	R	S	R	R
8	R	R	S	R	S	R	R	R	I	R
9	R	R	S	R	-	R	S	S	S	R
10	R	R	-	S	I	S	-	S	R	R
11	R	-	-	R	R	R	S	S	R	R
12	R	R	R	R	R	R	-	S	R	R
13	R	R	-	R	-	R	S	S	R	R
14	R	R	-	R	R	R	-	R	R	R
15	-	-	-	R	S	S	S	S	R	R
16	R	R	-	R	R	R	S	R	R	R
17	-	R	-	-	-	-	S	S	-	R

R: Resistant, S:Susceptible, I: Intermediate

Previous studies revealed a cumulative mortality rate of 52% in neonates and 33% in non-neonates with *E. meningoseptica* infections [10]. In the largest series of 118 patients with *E. meningoseptica* bacteremia at a medical center in Taiwan, the 14-day mortality rate was 23% [5]. The acquisition of the infection in an ICU was a significant predictor of mortality. These results all support previous findings by Lin et al. that host factors were the critical determinant in predicting outcomes [11]. Aldoghaim et al. reported that although most of the patients did not receive appropriate antibiotic treatment, the mortality rate in their study was low (16.5%), which was much lower than that reported in past studies [1,5,10]. In our study, the mortality rate was 29.4% and they were all from ICU. Only one of them was pediatric aged and died within 12 days after isolation of *E.meningoseptica* from endotracheal aspiration material because of septicemia. All of our adult patients have died; three of them had renal failure (all underwent hemodialysis), and one had cardiac arrest because of cerebrovascular disease. In addition, only one of the adult deaths in this study was related to *E.meningoseptica* septicemia (which underwent hemodialysis); while the other cultures were negative for *E.meningoseptica* when they died.

The choice of optimal antibiotic agents for the treatment of *E. meningoseptica* infection is difficult because of the unpredictability and breadth of antimicrobial resistance of this organism, which is often resistant to antibiotics prescribed for the treatment of serious gram-negative bacteria, such as β-lactam agents, aminoglycosides and carbapenems [1]. Lin et al. reported that 54.5% of patients infected with E. meningoseptica bacteremia recovered without receiving appropriate antibiotic treatment [11]. Aldoghaim et al. reported that in their study, among those receiving an inappropriate antibiotic for *E. meningoseptica* bacteremia, five of six patients recovered [1]. This may be attributable to the low virulence of *E. meningoseptica*. However, further studies are required to understand the virulence mechanisms of *E. meningoseptica*.

Chan et al. detected piperacillin/tazobactam as the most effective antibiotic (100% susceptibility) against *E. meningoseptica*, followed by, trimethoprim/sulfamethoxazole (78.6% susceptibility) and fluoroquinolones (87.5% susceptibility for levofloxacin and moxifloxacin and 33.3% susceptibility for ciprofloxacin) [3]. In a study, they treated all patients with injectible minocycline and co-trimoxazole (Narayan MD, Kumar AL, Kaushik M. Emergence of *Elizabethkingia meningoseptica* nosocomial infections and role of introvenous minocycline therapy. ECCMID Abstract Book. Copenhagen 2016; EVO166). Although some anecdotal reports have revealed the successful treatment of *E. meningoseptica* meningitis using a combination therapy of vancomycin with other antibiotics [12,13], the use of vancomycin is not suggested because of its high minimum inhibitory concentration [14,15,16].

With regard to antimicrobial susceptibility, we observed that *E. meningoseptica* strains showed resistance to carbapenems, aminoglycosides and β-lactam antibiotics, and sensitivity to cephoperazone/sulbactam, fluoroquinolones and trimethoprim/sulfamethoxazole. In contrast to previous studies [4,5,16,17], our isolates showed a lower susceptibility (18.1%) against piperacillin/tazobactam. This resistance pattern may be related to prolonged courses of antibiotics in these patients, which might lead to selective pressure for resistance in this organism. The present study has several limitations. It was a retrospective study, and missing data may have obscured potential risk factors that were not documented in medical records. Our sample size was small. However, a prospective study involving a significant number of patients will require many years of research. In addition, the factors of the pathogenicity, antimicrobial susceptibility and virulence of *E. meningoseptica* remain unclear. A well-designed prospective study may be required to address these limitations in the future.

In summary, this microorganism, which is resistant to antibiotics frequently used in the treatment of gram-negative infections, should be kept in mind for patients at risk group who do not respond to treatment. Once microbiologist suspected this infection, the clinician should immediately be informed so that appropriate antibiotic changes may be done early.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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